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A METHOD FOR IN VIVO REPAIR OF CARTILAGE DEFECTS OR BONE AND CARTILAGE DEFECTS IN JOINTS IN HUMANS

Field of invention

The present invention relates to a method and materials for in vivo repair of cartilage or bone and cartilage defects in joints in humans.

Background of the invention

More than one million arthroscopic procedures and total joint replacements are performed each year in the U.S. and Europe together. Included in these numbers are, for instance in the U.S., about 90,000 total knee replacements, and around 50,000 procedures for repairing defects in the knee alone per year (In: Praemer, A., Furner, S., Rice, D.P., Musculoskeletal Conditions in the United States, Park Ridge, Ill.: American Academy of Orthopaedic Surgeons, 1992, 125).

A method for regeneration-treatment of cartilage would be an advantage and could be performed at an earlier stage of a joint damage reducing the number of patients needing artificial joint replacement surgery. Previously, cleaning or resurfacing the cartilage structure have been attempted using subchondral drilling, abrasion, etc. whereby diseased cartilage and even subchondral bone is excised (Insall, J., Clin. Orthop. 1974,101,61; Ficat, R.P., et al., Clin Orthop. 1979, 144,74; Johnson, L.L., In: (McGinty, J.B., Ed.) Operative Arthroscopy, New York, Raven Press, 1991, 341).

Other methods such as suturing a periosteal flap (for instance removed from tibia) over the defect has been used either as a treatment procedure in itself, or has been used in combination with implantation of cultured (e.g., autologous) chondrocytes. The methods using this combination have in principal been developed by Brittberg and Peterson (Brittberg, M., et al., New Engl. J. Med., 1994,331,889).

Cells cultured using the methods described by Brittberg et al. are used for autologous implantation into knee joints of patients. Kurt Osther et al. have described, in U.S. patent No. 5,759,190, the use of a barrier towards bone that may be useable in osteoarthritis - type of lesions in theory, in order to prevent bleeding and proliferation of stem cells from the underlying denuded cancellous bone. The barrier is made of collagen type I.

Summary of the invention

The present invention refers to a method and materials for regenerative-treatment of cartilage and bone in humans.

Conditions that may be treated according to the present invention are conditions, such as osteoarthritis.and other cartilage and bone destructive conditions, e.g. osteochondritis dissecans(OCD).

The present invention relates to a method and materials, which are adapted to achieve an optimal hyalin articular cartilage as a result of cartilage repair. According to the invention, the environment with which implanted chondrocytes are in contact is especially designed to obtain a hyalin cartilage structure by securing that the chondrocytes integrin receptors are exposed to a certain motif, which will induce signal transduction in chondrocytes resulting in the chondrocytes producing and secreting matrix products which form hyalin cartilage. Hyalin cartilage is the cartilage naturally occurring in any movable joints in mammals as a thin layer that covers the ends of bones and is a hard, smooth, tough and elastic material. Opposing hyalin cartilage surfaces co-operating in a joint permit, in the presence of synovial fluid, a practically frictionless motion. Even thin layers of hyalin cartilage are capable of absorbing load forces five times the body weight. Hyalin cartilage in a joint is produced and maintained by a relatively small proportion, of the order of 1-5% by weight of the cartilage, of chondrocytes as the only living element. The hyalin articular cartilage structure is formed from matrix products, in particular collagen type II, which are secreted by chondrocytes when induced correctly. In the present context, the correct induction derives from certain proteins capable of presenting a particular recognition motif.

According to the invention, particular measure is taken to perform the cartilage repair using techniques and material, which secure that the chondrocytes are induced correctly.

One aspect of the invention relates to a method for in vivo repair of cartilage defects in joints, comprising

applying, over a cartilage-defect surface part of a joint, a membrane a first surface part of which facing the cartilage-defect surface carries a composition

comprising at least one substance which is capable of inducing signal transduction in chondrocytes resulting in the chondrocytes producing and secreting matrix products which form hyalin cartilage,

introducing, in the interstice between the first membrane surface part and the cartilage-defect surface, a suspension of chondrocytes,

and joining a rim part of the membrane to surrounding intact cartilage so as to sealingly entrap the chondrocyte suspension in the interstice, thereby allowing the condrocyte suspension to produce and secrete matrix products which form hyalin cartilage.

Another aspect of the present invention relates to the use of a composition comprising at least one substance, which is capable of inducing signal transduction in chondrocytes resulting in the chondrocytes producing and secreting matrix products which form hyalin cartilage for the preparation of a membrane carrying the composition on at least one surface part for use as an implantable surgical material for the repair of chondral or osteochronral defects or for implantation treatment of osteoarthrosis in humans.

Further aspects of the present invention will appear from the claims.

Brief description of the drawings

The present invention is further illustrated with reference to the drawings, wherein

Figure 1 shows one embodiment of the method or use according to the present invention.

Figure 2 shows another embodiment of the present invention applicable for the treatment of osteoarthritis.

Figure 3 shows yet another embodiment of the present invention using a membrane where both surfaces are impregnated the hyalin cartilage inducing substance.

Detailed description of the invention

The invention relates to a method and materials for in vivo repair of cartilage or bone and cartilage defects in joints in humans.

The cartilage-defect surface part of the joint is normally a surface part where the original cartilage had been torn apart. As a preparation for the repair, the defect is debrided so that the cartilage-defect surface part now appears as a cartilage-free indentation, often down to tidemark or calcified layer, the indentation being surrounded by healthy cartilage.

The membrane applied over the cartilage-defect and debrided area is normally adapted in size so that the rim part of the membrane can be sutured to the surrounding healthy cartilage. After application and suturing of the membrane, the edge of the membrane is normally sealed to the healthy surrounding cartilage by means of a suitable "glue", such as Tisseel, (Baxter Immuno Austria, a lyophilized, virus-inactivated substance that consists of fibrinogen, plasmafibronectin, factor VIII and plasminogen), which during application is mixed with aprotinin solution, thrombin 4, thrombin 500 and calcium chloride solution, using a dual syringe system connected to one blunt injection needle. The sealing is not completed; a small part of the circumference is left unsealed to allow for the implantation of chondrocytes (which may be introduced through the small, unsealed hole using a syringe with a blunt needle).

A first surface part of the membrane, normally the whole area of one of the surfaces of the membrane, carries the composition comprising at least one substance which is capable of inducing signal transduction in chrondrocytes resulting in the chrondrocytes producing and secreting such matrix products which form hyalin cartilage. The membrane may have been impregnated with the composition prior to use, or the composition may be applied directly prior to or directly after application of the membrane to the cartilage-defect surface part of the joint. The membrane is a non-immunogenic, non-toxic, biodegradable membrane. The membrane may be porous or substantially non-porous, but not with a dense structure, which would prevent chondrocytes from invading the membrane.

Alternatively, the chondrocyte suspension may be applied simultaneously with a solution containing the motif or motifs using a twin syringe.

A suitable membrane material may be a collagen type I. However, collagen type I in itself will tend to induce phenotypic change of the chondrocytes to fibroblasts or ostecytes, and it is therefore essential that any part of the membrane to be in contact with chondrocytes is not perceived by the chondro-

cytes as collagen type I, but rather as the composition used for the impregnation. The membrane should preferably be coated with a protein or protein composition that induces phenotypic maintenance of the chondrocytes, so that no shift towards fibroblasts or osteoblasts/osteocytes is induced. Chondrocytes, bone cells and fibroblasts are all from the same mesenchymal stem cell.

The impregnation or, generally, the application of the composition, may be performed in many conventional manners, such as spraying, painting or immersion. As stated above the application of the composition and the application of the chondrocytes may also be performed in a simultaneous way using a twin syringe. In an interesting embodiment, the structure of the membrane is one, which allows chondrocytes to adhere to and invade the entire membrane. This may, e.g., be obtained by using a membrane of a suitable porosity. By allowing the chondrocytes to invade through the membrane, a particularly smooth surface of cartilage, levelled to the surrounding cartilage, can be obtained.

The at least one substance of the composition capable of inducing the signal transduction is preferably a peptide or protein containing a motif recognised by integrin receptor sites of chondrocyte membranes, such as the sequence Arg-Gly-Asp (RGD).

A few definitions and explanations concerning cartilage, integrins and RGD recognition motif are given here:

Cartilage:

The biologic and mechanical properties of cartilage depend on the design of the tissue and the interaction between the chondrocytes and the matrix that maintains the tissue. Chondrocytes form the macromolecular framework of the tissue matrix from three (3) classes of molecules: collagens, proteoglycans, and non-collagenous proteins. Type II, IX, and XI collagens form a fibrillar network that gives the tissue the tensile stiffness and strength. Collagen type VI forms part of the matrix immediately surrounding the chondrocytes and help the chondrocytes to bind and attach to the framework of the matrix. Of the collagens, mentioned above, collagen type II is the most abundant (Gay, S. et al. Arthritis Rheum. (1980) 23,937; Mayne, R., Cartilage Collagens – what is their function, and are they involved in aticular disease? Arthritis Rheum. (1989) 32,241).

The large aggregating proteoglycans (aggregans) give the tissue its stiffness to compression. Small proteoglycans, decorin, biglycan and fibromodulin, bind to other matrix macromolecules and help stabilize the matrix. The non-collagenous proteins including anchorin CII, tenascin and fibronectin, helps chondrocytes to attach to the matrix (Hardingham, T. and Bayliss, M., Semin. Arthritis Rheum. (1990) 20,12; Hardingham, T., et al., Eur. J. Clin. Chem. Clin. Biochem. (1994) 32,249).

Integrins:

Chondrocytes express a number of cell-surface molecules that mediate cell-cell or cell-matrix interactions. It is well known that cellular interactions, such as cell adhesion, migration, invasion, between cells and the extracellular matrix are mediated by the integrin family of cell surface receptors (Sonnenberg, A., Integrins and their ligands. Curr. Top. Microbiol. Immunol. (1993), 184,35; Springer, T.A., Nature (1990) 346, 425).

Cell adhesive interactions play important roles during many normal physiological processes such as wound repair. Cell adhesion is mediated by the specific interactions of cell surface receptors with extracellular glycoproteins. The best described cell adhesion receptors are in fact the integrins which comprise a family of more than twenty three (23) non-covalent, heterodimeric complexes consisting of an alpha and a beta subunit non-covalent bound together (Salter, D.M., et al., Integrin expression by human articular chondrocytes, Br. J. Rheumatol. (1992) 31,231; Woods, V.L. et al., Arthritis Rheum. (1994), 37,537).

RGD motif:

The integrins interact with extracellular matrix molecules, serum constituents and the adhesion molecules of the immunoglobulin family. The extracellular domains of many integrins recognise the RGD tripeptide (Arg-Gly-Asp) found in several extracellular macromolecules such as Vitronectin, Fibronectin (type I,II or III) , Fibrinogen, Fibrillin (type I and II), Kistrin, Echistatin, Von Willebrand Factor (vWF) and in the bone matrix proteins such as Osteopontin (OPN, a very abundant protein in the bone) and Bone Sialoprotein (BSP).

RGD-containing proteins have been shown to be components of cartilage matrix. Cell attachment assays have shown the presence of integrins mediating binding of

chondrocytes to fibronectin in an RGD-dependent manner (Arner, E.C., et al., Arthritis Rheum. (1995) 38,1304).

Fibronectin:

The best characterised of the integrin ligands is fibronectin. Fibronectin has at least 2 independent cell adhesive regions: one located near the centre of the polypeptide chain in the 9. and 10. Type III modules binds to the alpha 5 beta 1 integrin. The biological function of the central cell adhesive region requires 2 critical amino acid sequences - an Arg-Gly-Asp (RGD) sequence and a Pro-His-Ser-Arg-Asn (PHSRN) sequence, which function in synergy for optimal binding to the alpha 5 beta 1 integrin. The spacing between the crucial RGD and PHSRN sequences is also important for activity, suggesting that the individual sequences alone are necessary, but not sufficient, to account for cell adhesive activity of fibronectin.

Although many integrins can bind fibronectin, the alpha 5, beta1 integrin is the major fibronectin receptor on most cells including chondrocytes. This integrin mediates cellular responses to e.g., fibronectin substrates as adhesion, migration, assembly of extracellular matrix, and signal transduction (Salter, D.M., et al., Br. J. Rheumatol.(1992) 31,231; Woods, V.L. Arthritis Rheum. (1994) 37,537).

In the method of the invention, the motif recognised by integrin receptor sites of chondrocyte membranes is preferably the sequence Arg-Gly-Asp (RGD). RGD is known to be recognised by various cells, including chondrocytes, and is known to induce such signal transduction that results in the correct matrix production that delivers building components for hyalin articular cartilage. However, to the knowledge of the inventors, it has never been suggested to utilise this phenomenon in chondrocyte implantation.

It will be understood that any other motif or sequence, which has the same or substantially induction capability as RGD could also be used in the method of the invention. The suitability of a motif or sequence for the purpose can be evaluated by incubating cultured chrondrocytes with a candidate substance followed by preparation of the cells for electron microscopy, and studying the chondrocytes at a suitable magnification; chondrocytes capable of secreting matrix products can easily be recognised in the this way because of their particular structure including cupula present in the membranes of the chondrocytes.

Thus, suitable substances of the composition are peptides or proteins showing the RGD motif. The peptides or proteins may be naturally occurring or synthetically prepared ones and more specifically biodegradable natural or synthetic polymers. Alternatively the peptide or peptides may be attached to a support.

While a substance or substances showing the above-mentioned motif inducing the secretion of the correct building stones of hyalin cartilage constitute a compulsory constitutent or compulsory constitutents carried by the coated or impregnated membrane, it is advantageous that the at least one peptide or protein of the composition contains a further sequence recognised by receptor sites of chondrocyte membranes. The further sequence is preferably the sequence Pro-His-Ser-Arg-Asn (PHSRN).

In many cases, it is preferred that the motif and the further sequence are carried on the same peptide or protein. Examples of proteins showing both the RGD motif and the sequence PHSRN are collagen proteins such as types II, VI, IX, and XI, , proteoglycans such as aggregans, decorin, fibromodulin and biglycan, and non-collageneous proteins such as cryoprecipitate, fibronectin, vitronectin, fibronogen, fibrillin, kistrin, echistatin, von Willebrand factor, tenascin and anchorin CII.

It is especiallly preferred that the protein is collagen type II or fibronectin. Further preferred is a composition carrying the motif or motifs.

In addition to the membrane carrying the composition which is capable of inducing signal transduction in chondrocytes resulting in the chondrocytes producing and secreting matrix products which form hyalin cartilage, it may be preferable to apply such a composition on the cartilage-defect surface prior to the application of the coated membrane, to thereby increase the intensity of the exposure of the implanted chondrocytes to the motif, as well as the capability of the implanted cells to bind with the surrounding chondrocytes and cartilage.

In this and other embodiments of the invention, some of the chondrocytes to be implanted can be included in the composition carried by the membrane and optionally applied directly on the cartilage defect in order to obtain a lining of cells resulting in a normal cartilage surface layer and transitional layer.

It is also possible to add, to the chondrocyte suspension to be implanted, a suitable concentration of a substance providing the inducing motif and optionally the additional sequence, such as one of the substances discussed above, in particular fibronectin or preferably collagen type II, to thereby increase the exposure of the implanted chondrocytes to the correct induction. The suitable concentration will normally be in the range of 10-30% of the total suspension, calculated on dry weight of e.g. collagen type II related to the total wet weight of the suspension.

Examples of conditions resulting in cartilage defects, which may be treated according to the present invention are chondreal leasions or ostochondreal lesions, osteochondritis dissecans (OCD), chondromalacia and ostearthritis.

The condition OCD, which is mainly appearing in children and teenagers, leaves a thickened retained cartilage of the affected focal area, which then loosens and becomes a fragment, and an osteochondritis dissecans (OCD) defect appears in the joints as seen in figure 2 below. However, the cause for the disorder is sometimes more complex. OCD has appeared to develop lesions where the condition prior to OCD has not been a thickening of the cartilage, but seems to have developed after an enchondral ossification has been complete, and where the cartilage surface has appeared normal in thickness.

Occurrence of subchondral cystic lesions, also called bone cysts or osseous cyst-like lesions is commonly recognised abnormalities of bones and joints that may or may not cause lameness. The most troublesome cysts are articular cysts. Controversy exists as to whether these lesions are a manifestation osteochondritis secondary to a joint trauma, or a combination of stress and trauma.

The method and materials according to the present invention can be used for regenerative treatment in all these conditions.

A particular embodiment of the invention permits a combined repair of both bone and cartilage. This embodiment utilises two membranes. Beneath the first membrane and over the denuded bone, e.g. seen in patients with osteoarthritis, bone cells are introduced, facing a surface of the membrane, which will promote bone growth. Between the first membrane and a second membrane covering the defect, a chondrocyte suspension is implanted, the chondrocytes facing the upper surface of the first membrane and the lower surface of the

second membrane, both of which contain a composition, which will induce the correct matrix production.

Thus, this embodiment of the invention constitutes a method for in vivo repair of bone and cartilage defects in joints, such as in osteoarthritic joints, comprising

applying, over a bone- and cartilage-defect surface part of a joint, a porous first membrane a first surface part of which facing the bone surface part consists of or carries a substance having substantially the growth-promoting effect on bone cells as collagen type I, such as collagen type I, and the opposite second surface part of which carries a composition comprising at least one substance which is capable of inducing signal transduction in chondrocytes resulting in the chondrocytes producing and secreting matrix products which form hyalin cartilage,

introducing, in the interstice between the first membrane surface part and the bone, a suspension of bone cells,

joining a rim part of the membrane to surrounding intact cartilage and/or bone so as to sealingly entrap the bone cell suspension in the interstice,

applying, over the first membrane, a second membrane a first surface part of which facing the second surface part of the first membrane carries a composition comprising at least one substance which is capable of inducing signal transduction in chondrocytes resulting in the chondrocytes producing and secreting matrix products which form hyalin cartilage,

introducing, in the interstice between the two membranes, a suspension of chondrocytes

joining a rim part of the membrane to surrounding intact cartilage so as to sealingly entrap the chondrocyte suspension in the interstice, thereby allowing the condrocyte suspension to produce and secrete matrix products which form hyalin cartilage

and allowing the bone cells to cover the osteoarthritic bone and to grow into the first membrane and the chondrocyte suspension to produce and secrete matrix

products which form hyalin cartilage and chondrocytes to adhere to the second surface part of the first membrane.

The chondrocytes adhering to the second surface part of the first membrane and the bone cells are preferably allowed to eventually form a transition layer between healthy bone cells and cartilage implant in that the first membrane allows bone cells to grow into the structure of the membrane from below, and chondrocytes to adhere to and grow into the membrane from above. Thereby, transition is obtained between healthy bone cells and healthy chondrocytes.

In any of the above-described embodiments, it is preferred that the cells implanted are autologous. Bone and cartilage tissues are harvested and enzyme-treated according to known methods.

The cell suspensions used are suitably cultures of the cells in question. The culturing of chondrocytes may be performed using known methods, as disclosed, e.g., by Brittberg et al. loc. cit. The culturing of bone cells may be performed using known methods, the culture medium being, e.g., Dulbecco MEM/HAM 12 with 10-20% foetal calf serum.

The cell cultures may be used as such as the suspensions implanted, or the cultures may be admixed with suitable media containing the patient's own serum at a concentration of, e.g., 10-20% vol/vol, thereby minimising immunogenic reactions. As an alternative or supplement to this, a motif-providing substance or composition of the kind described above, such as collagen type II for chondrocyte suspensions and collagen type I for bone cell suspensions, may be added prior to implanting the suspension.

When using titan constructions in joint replacement etc. it would, in accordance with the present invention, be possible to apply cultures of chondrocytes directly onto an irregular or rough titan surface to thereby fix the chondrocytes to said surface.

The principles of the invention are further illustrated in the appended drawings.

CLAIMS

1. A method for in vivo repair of cartilage defects in joints in humans, comprising

applying, over a cartilage-defect surface part of a joint, a membrane a first surface part of which facing the cartilage-defect surface carries a composition comprising at least one substance which is capable of inducing signal transduction in chondrocytes resulting in the chondrocytes producing and secreting matrix products which form hyalin cartilage,

introducing, in the interstice between the first membrane surface part and the cartilage-defect surface, a suspension of chondrocytes,

and joining a rim part of the membrane to surrounding intact cartilage so as to sealingly entrap the chondrocyte suspension in the interstice, thereby allowing the condrocyte suspension to produce and secrete matrix products which form hyalin cartilage.

2. A method according to claim 1, wherein the membrane is a non-immunogenic, non toxic, biodegradable membrane which is optionally of a structure which allows chondrocytes to adhere and invade the entire membrane.

3. A method according to claim 1 or 2, wherein the composition comprises at least one peptide or protein containing a motif recognised by integrin receptor sites of chondrocyte membranes.

4. A method according to claim 3, wherein the motif is the sequence Arg-Gly-Asp (RGD).

5. A method according to claim 3 or 4, wherein the at least one peptide or protein of the composition contains a further sequence recognised by receptor sites of chondrocyte membranes.

6. A method according to claim 5, wherein the further sequence is the sequence Pro-His-Ser-Arg-Asn (PHSRN).

7. A method according to claim 5 or 6, wherein the motif and the furthet sequence are carried on the same peptide or protein.

8. A method according to any of claims 3-7, wherein the protein is selected from collagen proteins such as types II, VI, IX, and XI, , proteoglycans such as aggregans, decorin, fibromodulin and biglycan, and non-collageneous proteins such as cryoprecipitate, fibronectin, vitronectin, fibronogen, fibrillin, kistrin, echistatin, von Willebrand factor, tenascin and anchorin CII.

9. A method according to claim 8, wherein the protein is collagen type II.

10. A method according to claim 8, wherein the protein is fibronectin.

11. A method according to any of the preceding claims, wherein a composition which is capable of inducing signal transduction in chondrocytes resulting in the chondrocytes producing and secreting matrix products which form hyalin cartilage is applied on the cartilage-defect surface prior to the application of the coated membrane.

12. A method according to claim 11, wherein the composition is a composition as characterised in any of claims 3-10.

13. A method for in vivo repair of bone and cartilage defects in joints in humans, such as in osteoarthritic joints, comprising

applying, over a bone- and cartilage-defect surface part of a joint, a porous first membrane a first surface part of which facing the bone surface part consists of carries a substance having substantially the growth-promoting effect on bone cells as collagen type I, such as collagen type I, and the opposite second surface part of which carries a composition comprising at least one substance which is capable of inducing signal transduction in chondrocytes resulting in the chondrocytes producing and secreting matrix products which form hyalin cartilage,

introducing, in the interstice between the first membrane surface part and the bone, a suspension of bone cells,

joining a rim part of the membrane to surrounding intact cartilage and/or bone so as to sealingly entrap the bone cell suspension in the interstice,

applying, over the first membrane, a second membrane a first surface part of which facing the second surface part of the first membrane carries a composition comprising at least one substance which is capable of inducing signal transduction in chondrocytes resulting in the chondrocytes producing and secreting matrix products which form hyalin cartilage,

introducing, in the interstice between the two membranes, a suspension of chondrocytes

joining a rim part of the membrane to surrounding intact cartilage so as to sealingly entrap the chondrocyte suspension in the interstice, thereby allowing the condrocyte suspension to produce and secrete matrix products which form hyalin cartilage

and allowing the bone cells to cover the osteoarthritic bone and to grow into the first membrane and the chondrocyte suspension to produce and secrete matrix products which form hyalin cartilage and chondrocytes to adhere to the second surface part of the first membrane.

14. A method according to claim 13, wherein the chondrocytes adhering to the second surface part of the first membrane and the bone cells are allowed to eventually form a transition layer between healthy bone cells and cartilage implant.

15. A method according to claim 13 or 14, wherein each composition is a composition as characterised in any of claims 3-10.

16. A method according to any of the preceding claims, wherein the chondrocytes suspension is a suspension of autologous chrondrocytes.

17. A method according any of claims 13-16, wherein the bone cell suspension is a suspension of autologous bone cells.

18. A membrane at least a surface part of which carries a composition comprising at least one substance which is capable of inducing signal trans-

duction in chondrocytes resulting in the chondrocytes producing and secreting matrix products which form hyalin cartilage.

19. A membrane according to claim 18, which is a non-immunogenic, non-toxid, biodegradable membrane.

20. A membrane according to claim 18 or 19, wherein the membrane material is collagen type I.

21. A membrane according to claim 18 or 19, wherein the membrane material is a biodegradable synthetic polymer.

22. A membrane according to any of claims 18 – 21, for use as an implantable surgical material for the repair of chondral or osteochronral defects or implantation treatment of osteoarthrosis.

23. The use of a composition comprising at least one substance which is capable of inducing signal transduction in chondrocytes resulting in the chondrocytes producing and secreting matrix products which form hyalin cartilage for the preparation of a membrane carrying the composition on at least one surface part for use as an implantable surgical material for the repair of chondral or osteochronral defects or for implantation treatment of osteoarthrosis in humans.

24. The use of a substance which is capable of inducing signal transduction in chondrocytes resulting in the chondrocytes producing and secreting matrix products which form hyalin cartilage for the preparation of a membrane carrying the composition on at least one surface part for use as an implantable surgical material for the repair of chondral or osteochronral defects or for implantation treatment of osteoarthrosis in humans.

25. The use of a substance which is capable of inducing signal transduction in chondrocytes resulting in the chondrocytes producing and secreting matrix products which form hyalin cartilage for the preparation of a composition for application to a membrane to be implanted as a surgical material for the repair of chondral or osteochronral defects or for implantation treatment of osteoarthrosis in humans.

26. The use according to any of claims 23-25, wherein the membrane is to be used as described in any of the claims 1-17.

27. The use of a chondrocyte culture for the preparation of a suspension for introduction into an interstice between a cartilage-defect surface part of a joint and a membrane surface carrying a composition comprising at least one substance which is capable of inducing signal transduction in chondrocytes resulting in the chondrocytes producing and secreting matrix products which form hyalin cartilage in humans.

28. The use according to claim 27, wherein the chondrocyte culture is a culture of autologous chondrocytes.

29. The use of a bone cell culture for the preparation of a suspension for introduction into an interstice between a bone- and cartilage-defect surface part of a joint and a surface part of a porous membrane, the surface part consisting of or carrying a substance having substantially the growth-promoting effect on bone cells as collagen type I, such as collagen type I.

30. The use according to claim 29, wherein the opposite surface part of the membrane carries a composition comprising at least one substance which is capable of inducing signal transduction in chondrocytes resulting in the chondrocytes producing and secreting matrix products which form hyalin cartilage.

31. The use according to claim 29 or 30, wherein the bone cell culture is a culture of autologous bone cells.

ABSTRACT

The present invention relates to a method and materials for in vivo repair of cartilage or bone and cartilage defects in joints in humans. The invention involves a membrane carrying a composition comprising at least one substance, which is capable of inducing signal transduction in chondrocytes resulting in the chondrocytes producing and secreting matrix products which form hyalin cartilage. The membrane is applied over a cartilage-defect surface part of a joint and a suspension of chondrocytes is introduced between the membrane and the cartilage-defect surface.

Figure 1
Autologous Chondrocytes – Collagen type II or Crude Cryoprecipitate or Fibronectin Induced

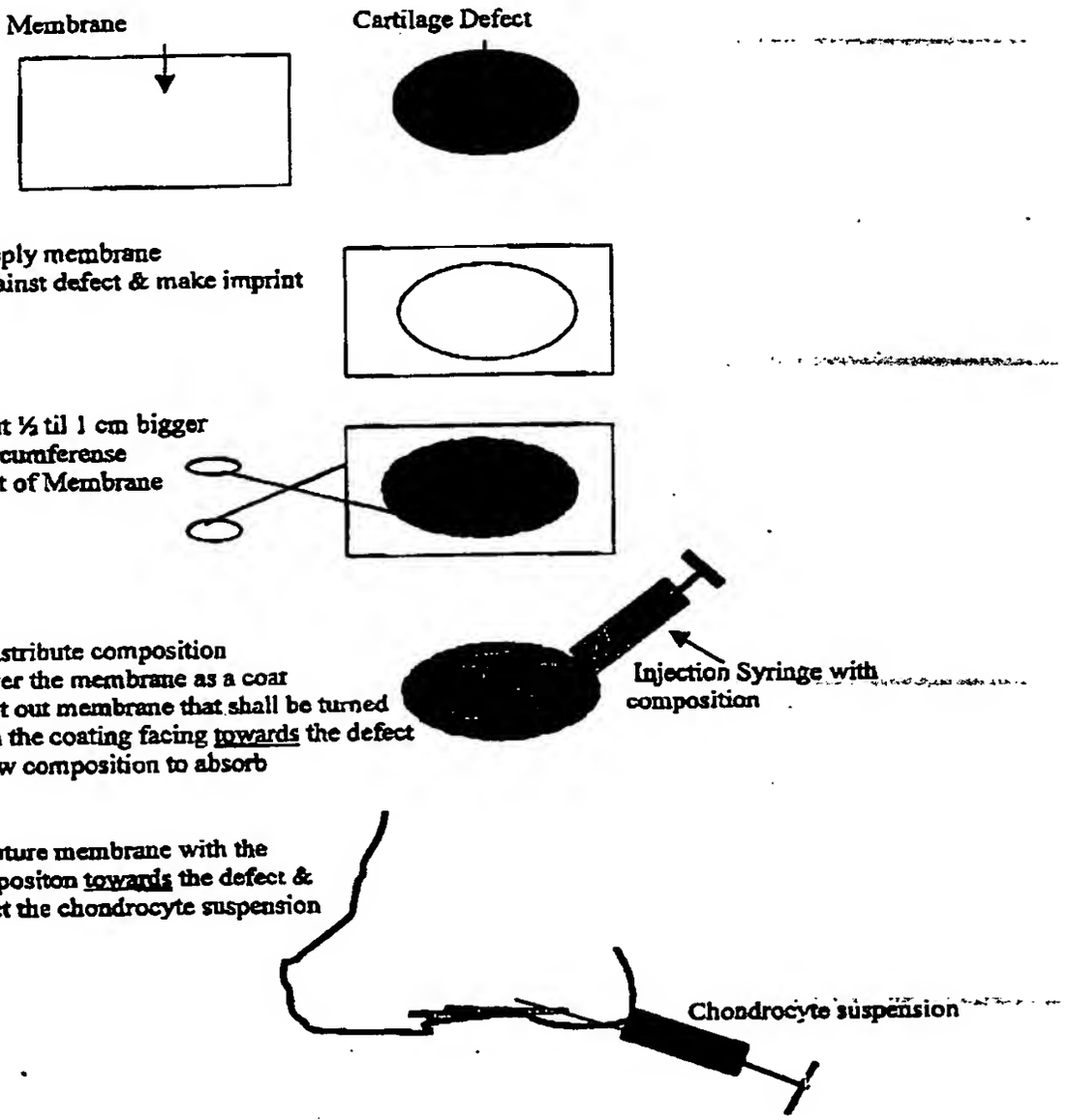
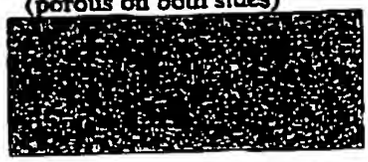


Figure 2

TREATMENT OF OSTEOARTHRITIS

1. Application of osteoblasts on the porous surface of special first membrane
2.

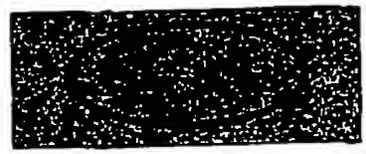
Special first membrane
(porous on both sides)



O.A. Defect

[RDG motif coated on one side (away from defect and imprint)]

2. Make imprint of defect in bottom



3. Cut out imprint (½ to 1 cm larger)

4. Place imprint in sterile Petri dish, apply Tisseel on imprint and distribute cultured immediately distribute cultured osteoblasts on Tisseel coated imprint

Distribution of Tisseel

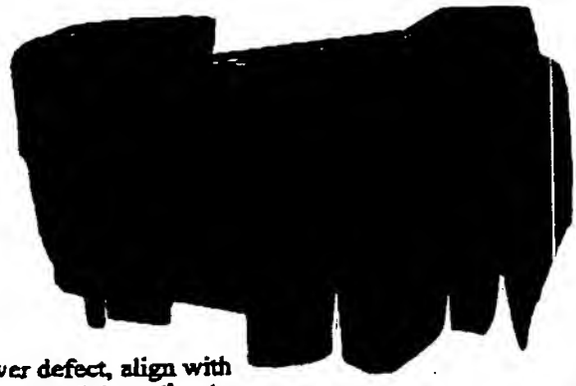
Distribution of osteoblasts

5. Leave osteoblasts on Tisseel coat for 2 minutes at room temperature

Figure 2, continued

TREATMENT OF OSTEOARTHRITIS

6. Place imprint, with osteoblast coat towards defect and RGD motif coat towards space for injected chondrocytes



7. Place second membrane over defect, align with surrounding cartilage and fasten. Inject chondrocytes into the cavity over the porous double coated membrane under which the osteoblasts are located

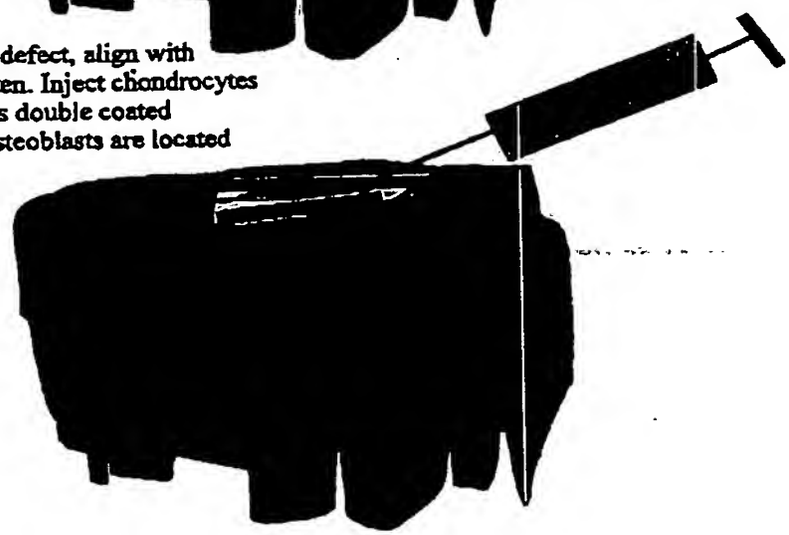
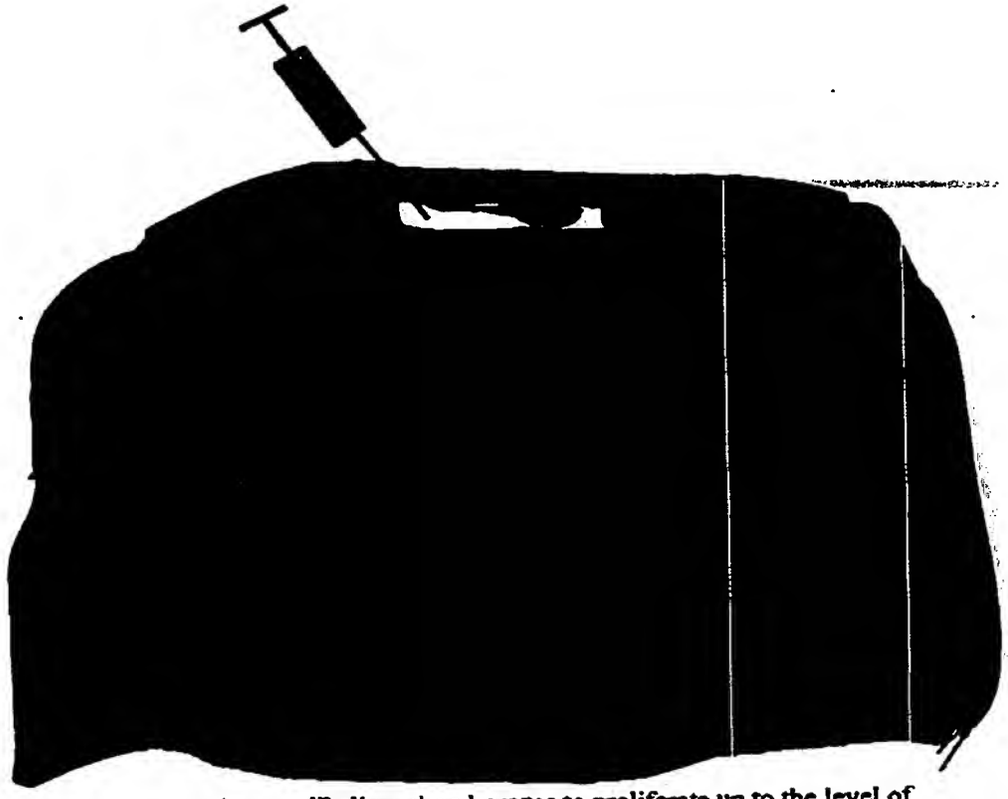


Figure 3

The use of the membrane, which is made porous on both the upper and the lower side of the membrane. The lower side of the membrane turning towards the defect (light orange) is coated with the RGD motif turning any matrix to a chondrocyte inducer for further matrix production and adhesion. The upper side of the membrane is also impregnated with RGD motif and is, as observed on the drawing, perforated or porous as is the lower part of the membrane. Chondrocytes are infused below the double porous membrane.



The perforated or porous membrane will allow chondrocytes to proliferate up to the level of the neighbouring surface. When the patient is placed in a CPM (Continuous Passive Movement) machine immediately after the implantation the implanted chondrocytes will be exposed to the same pumping mechanism that occurs over the neighboring healthy cartilage. In theory the pumping mechanism and the movement of the joint will decide the layering of cells.